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IS AN ADDITIONAL UNCERTAINTY FACTOR NECESSARY AND APPROPRIATE TO ASSESS PRE- AND POST-NATAL DEVELOPMENTAL AND REPRODUCTIVE EFFECTS IN INFANTS AND CHILDREN EXPOSED TO PESTICIDES THRU CHRONIC DIETARY EXPOSURE?

Executive Summary

This position paper summarizes the Office of Pesticide Program's (OPP) response to the legislative requirements of the Food Quality Protection Act (FQPA) of 1996, on the basis of the recommendation in the NAS Kid's Study (NRC, 1993), that an additional uncertainty (up to 10-fold) factor be used in the Agency's risk assessment practices. NRC concluded that infants and children may have significantly different exposures and/or responses to pesticides than adults. Thus it was believed that an additional uncertainty factor may in some cases be needed to account for the lack or incompleteness of pre- and post-natal developmental toxicity data. The Agency generally agrees that for certain situations, specifically, an incomplete data base, the use of such an additional uncertainty factor is appropriate. Other situations, e.g., where it is known or expected that the human population is more sensitive than experimental animals to an agent, must be considered on a case-by-case basis. While use of an additional uncertainty factor in every case appears to be unwarranted and was not recommended by the NAS, several additional steps appear appropriate. These steps include 1) finalization of the revised multi-generation reproduction and prenatal developmental toxicity test guidelines, with their improved consideration of the unique sensitivities of the developing fetus and maturing individual, and 2)continued collaboration with ORD, other Agencies and stakeholders to develop protocols to evaluate the direct pre-weaning effects of chemicals on the neonate/infant, and 3)continue to support the development and execution of a research plan to characterize age-related differences which may exist as a consequence of exposure to pesticides. The Agency believes that the approach described in this paper is consistent with both the 1993 NAS report and the August 1996 FQPA.

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I. Background

In 1988, the U.S. Congress asked the National Academy of Sciences (NAS) to evaluate the Agency's existing risk assessment practices to determine whether or not they adequately considered the potential for risks to infants and children. In 1993, the NAS published its report on Pesticides in the Diets of Infants and Children (NRC, 1993) in which it concluded that infants and children may have significantly different exposures and/or responses to pesticides than adults. Because of these and other differences, the NAS made recommendations regarding tolerance-setting, toxicity testing (cancer, reproductive and developmental toxicity, neurotoxicity, immunotoxicity and hormonal effects), uncertainty factors, food consumption data, pesticide residue data, and risk assessment.

In August 1996 Congress passed new pesticide food safety legislation, the Food Quality Protection Act (FQPA; P.L. 104-170). The amendments to the FFDCA in this legislation have directly incorporated the NAS report's recommendations [1] regarding special protections for infants and children. The FQPA states [FFDCA § 408(b)(2)(C)(I)(I)], "In the case of threshold effects, for purposes of clause(ii)(I)(reasonable certainty that no harm will result) an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirements for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children."

This paper presents how the Agency currently addresses potential hazards associated with pesticide exposure to infants and children for chronic dietary risk assessment with regard to the

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[1] The NAS report (1993) states in its executive summary, "Because there exist specific periods of vulnerability during postnatal development, the committee recommends that an uncertainty factor up to the 10-fold factor traditionally used by EPA and FDA for fetal developmental toxicity should also be considered when there is evidence of postnatal developmental toxicity and when toxicity testing relative to children are incomplete. The committee wishes to emphasize that this is not a new, additional uncertainty factor but, rather, an extended application of an uncertainty factor now routinely used by the agencies for a narrower purpose.

In the absence of data to the contrary, there should be a presumption of greater toxicity to infants and children. To validate, this presumption, the sensitivity of mature and immature individuals should be studied systematically to expand the current limited data base on relative sensitivity."(pp. 9, 10)

use of uncertainty factors (UF) in deriving the reference dose (RfD). The scope of this paper is limited to describing how OPP utilizes data including those related to pre- and post-natal reproductive/developmental toxicity and how it considers incomplete data sets when making the reference dose determination. [2]

The paper also provides recommendations for improving the Agency's ability to assess these hazards. Furthermore, it should be noted that there may be a need to consider the use of an additional uncertainty factor when estimating the margin of exposure based on the uncertainties and assumptions made regarding exposure in order to make risk management decisions. The Agency is currently evaluating the need to develop interim guidance on this point which may be used for assessing aggregate exposure.

II. OPP's Current Practice for Assessing Threshold Non-linear Effects of Pesticides

The concept of using the available toxicity data base required for food use pesticides along with appropriate safety or uncertainty factors to establish an upper limit for human dietary exposure to pesticides has been practiced for more than 30 years. The term Reference Dose (RfD) or the older term, acceptable daily intake (ADI), refers to an approximate amount of pesticide which, if ingested daily over a human's entire lifetime, appears to be without appreciable risk.

OPP's guidance paper (USEPA, 1985) stated that the following data must be present to establish a reference dose: (1) a chronic rat feeding study, (2) a chronic dog study, (3) a rat multi-generation reproduction study and (4) two developmental toxicity studies in different species, usually rat and rabbit.

If all these studies are present, the RfD is calculated by dividing the most appropriate NOEL (usually the lowest NOEL) by 100 after a weight of the evidence peer review by senior scientists in OPP. The 100 fold uncertainty factor is based on the assumption that there can be variations in sensitivity. Therefore OPP applies 10 for interspecies and 10 for intraspecies variability. In the absence of a chronic dog, chronic rat or

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[2] The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime (U.S. EPA, 1991a)

reproduction study (or studies), additional uncertainty factors may be used. For example, if a chronic dog study is missing, then an additional factor of 3 may be used to account for the fact that the NOEL from the dog study may be lower than the NOELs of either the chronic rat or the reproduction studies. If two of these three major studies are missing, the additional factor may be 10.

Likewise, additional factors may be used to account for the lack of a NOEL in a critical study which may form the basis for the RfD. Depending on the severity of the effect, additional factors may range from 3 to 10.

The NAS report (NRC, 1993) recommended consideration of an extra uncertainty factor when there is evidence of developmental toxicity but data are incomplete. EPA and FDA take a weight of the evidence approach based on the severity and nature of the effect, and the presence or absence of maternal toxicity in determining what uncertainty factors to apply. Furthermore, neither the OPP Standard Evaluation Procedures (draft) nor the Agency risk assessment guidelines concerning developmental and reproductive toxicity recommend an extra uncertainty factor. FDA in l984-5 formulated a policy [3] for requiring an additional 10-fold safety factor for food and color additives which demonstrated irreversible developmental effects such as malformations (T. Collins/FDA, 1995, personal communication). Usually an uncertainty factor of 100 is applied to NOELs in animal studies, and is considered sufficient to protect human populations from developmental effects (Newman et al., 1993; U.S. EPA, 1991b; Wilson, 1973). Wilson (1973) noted that only in extreme cases, e.g. chemicals without beneficial properties, should a larger uncertainty factor be recommended.

Although not used for risk assessment purposes, an extra 10-fold factor is consistently applied to NOELs for developmental/ reproductive endpoints for chemicals identified under California's Proposition 65. This factor is part of the law and is not ordinarily used in the risk assessment process by California's Environmental Protection Agency (CalEPA). In fact, CalEPA normally uses a 100-fold uncertainty factor when performing a risk assessment based on a NOEL for a developmental endpoint. The 1000-fold uncertainty factor is used to trigger the public information requirement contained in the law (personal communication between Ruby Reed, CalEPA, and Reto Engler, USEPA).

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[3] This policy relates to developmental findings in the two generation reproduction studies in association with a teratology phase conducted with oral (dietary, drinking water) exposure and includes decreases in litter size, increased resorptions, increases in malformations, increased still births (Jackson, 1988; Kokoski, 1990).

Circumstances which may trigger EPA's use of an additional uncertainty factor in OPP include: 1) scenarios which lack an exposure model for individuals who may be more sensitive than the test animals [4] (Hemminki and Vineis, 1985; Kimmel et al., 1984; SAB, 1995; Tilson et al., 1990) and 2) the toxic properties are such that "extrapolation" from the dose-response curve [5] is difficult. Elevations in human background exposure to xenobiotics (e.g., pollutants such as methlymercury, PCBs, hormonally active agents) (SAB, 1995; Tilson, 1990; Wilson, 1973) should also be taken into consideration in exposure estimates but not necessarily in the application of uncertainty factors. Principles used by the WHO Expert Panel of the Joint Meeting on Pesticide Residues (JMPR)(WHO, 1990) in modifications of the 100-fold UF are presented in Appendix 1.

Currently when OPP determines the appropriate uncertainty factors, it weighs all of the following elements:

1) completeness of the toxicological database for laboratory animals
2) results of human studies
3) slope of the dose response curve
4) severity of the effects
5) known susceptibility and exposure of the target human population
6) what is known about metabolic considerations
7) as well as structure activity relationships between the pesticide in question and any known human developmental toxicants.

III. Case Studies Illustrating Current Practices

The following examples are given to illustrate OPP's current practices with regard to pre- and post-natal data from the standard battery of toxicity tests required for food use chemicals and the establishment of the RfD for chronic dietary exposure. These examples are intended to represent OPP decision logic for establishing a reference dose.

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[4] Generally, such factors as nutrition, personal habits (e.g., smoking, alcohol consumption, illicit drug abuse), or pre-existing disease (e.g., diabetes) may predispose some individuals to be more sensitive to developmental effects of various agents (EPA, 1991; p. 63820).

[5] The total size of the uncertainty factor will vary from agent to agent and will require the exercise of scientific judgement, taking into account interspecies differences, variability within species, the slope of the dose-response curve, the background incidence of the effects, the route of administration, and pharmacokinetic data (EPA, 1991b; p. 63819).

3 a. Case 1: The use of an extra uncertainty factor

In Case 1, a complete toxicological data base was available and acceptable. The OPP RfD Committee recommended that a RfD be established based on the reproductive toxicity study in rats (dose levels of 0, 200, 500 or 700 ppm) with a reproductive toxicity NOEL of 200 ppm (14 mg/kg/day in males and 16 mg/kg/day in females). At the next higher dose level of 500 ppm (33 and 44 mg/kg/day, males and females, respectively), the following effects were observed: decreased maternal body weight and/or body weight gain during gestation in both generations (P, F1), reduced pre-mating body weight gains in the second generation (F1 adults), increased duration of gestation in both F1 and F2 dams, reduced prenatal viability (fetal and litter), reduced litter size, increased number of stillborn pups, reduced pup and litter postnatal survival, and decreased pup body weights throughout lactation. Male fertility was reduced in the F1 generation at 500 and 700 ppm, with degeneration and/or atrophy of the germinal epithelium of the testes and oligospermia and intra tubular degeneration of seminal product in the epididymides. In addition, developmental toxicity was observed in the rat at 25 mg/kg/day evidenced as decreased fetal weights and increased variations. The NOEL for developmental toxicity in the rat was 10 mg/kg/day. **An uncertainty factor (UF) of 100 was applied to the NOEL of 14 mg/kg/day account for interspecies extrapolation (10) and intraspecies variability (10) and an additional uncertainty factor (UF) of 3 was applied to account for the nature and severity of effects noted in the reproduction study and pre-natal effects noted in the developmental toxicity studies at treatment levels that were not maternally toxic. The RfD was estimated to be 0.05 mg/kg/day.**

3 b. Case 2: No additional UF required for RfD

In Case 2, a complete toxicological data base was available and acceptable. The OPP RfD Committee recommended that a reference dose for this chemical be based on the 1 year feeding study in dogs (dose levels of 0, 15, 50, 250 or 1500 ppm) with a systemic NOEL of 50 ppm (1.9 and 1.6 mg/kg/day, males and females, respectively). Males showed growth retardation at 250 ppm (8.9 mg/kg/day) and 1500 ppm (55.8 mg/kg/day). Both sexes at these dose levels (7.0 and 50.0 mg/kg/day for females, respectively) exhibited decreases in RBC, HCT and HGB, increases in Heinz bodies, methemoglobin, MCV, MCH, reticulocytes, platelets, plasma total bilirubin, spleen weight and spleen/body weight ratio and liver weight and liver/body weight ratio. Hematopoiesis and sinusoidal engorgement occurred in the spleen and hyperplasia

occurred in the marrow of the femur and sternum. The liver showed an increased pigment in the Kupffer cells. **An uncertainty factor (UF) of 100 was applied to the NOEL of 1.6 mg/kg/day to account for interspecies extrapolation (10) and intraspecies variability (10). On this basis, the RfD was calculated to be 0.016 mg/kg/day. The NOEL for reproductive effects for this chemical was 15 mg/kg/day, which is approximately ten fold higher than the NOEL used for the RfD; the LOEL for reproductive effects was 163 mg/kg/day based on decreased number of viable pups on day 4. The NOEL for developmental toxicity in both species tested (rat and rabbit) was greater than the limit dose of 1000 mg/kg/day. Therefore, the use of an additional UF for reproductive/developmental effects was not warranted.**

3c. Case 3: RfD set on reproductive data and which does not warrant an extra UF

Case 3 has a complete toxicological data base which was considered acceptable by the RfD Committee. The RfD is based on a three-generation reproduction study (dose levels of 0, 1000 or 10,000 ppm) in which the LOEL for offspring systemic toxicity is 10,000 ppm (661 mg/kg/day) based on reduced pup body weights late in lactation. **The OPP RfD Committee recommended that the reference dose be based on the reproductive toxicity study with a NOEL of 63 mg/kg/day (1000 ppm). The NOEL for developmental effects in one species (rat) was greater than 1000 mg/kg/day. The NOEL for developmental toxicity in the rabbit was 40 mg/kg/day. The LOEL in the rabbit developmental toxicity study was 200 mg/kg/day based on increased resorptions. Because the NOELs for the rabbit developmental toxicity and reproduction studies were similar, the Agency used the NOEL from the reproduction study. The NOEL from the reproduction study was used to set the reference dose because the route of exposure was dietary which was deemed more appropriate for a chronic dietary risk assessment than short term gavage dosing (which is the method of exposure in the developmental toxicity study). An uncertainty factor (UF) of 100 was applied to account for both interspecies extrapolation (10) and intraspecies variability (10). Even though this was a reproduction study, the Committee believed that an UF of 100 was adequate in view of the fact that the only effect observed was decreased pup body weight at a dose that was ten times the NOEL.**

IV. Apparent Strengths and Weaknesses of the EPA's Testing Paradigm in Protecting Infants and Children.

The current Agency practices for developing a chronic dietary risk assessment take into account an overall weight of evidence of the toxicological data. Pre- and post-natal data are a subset of the comprehensive [6] toxicological database for food use chemicals. Nevertheless, the NAS report asserted (NRC, 1993; p.4),"...little work has been done to identify effects that develop after a long latent period or to investigate the effects

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For food use chemicals an extensive amount of toxicology data is provided which addresses multiple routes of exposure (oral, dermal, inhalation) and varying lengths of exposure (acute, short term, subchronic, chronic) and age groups (fetal, neonates, pups, young, mature and old), multiple species (rat, mouse, dog, rabbit), male and females, pregnant and non-pregnant animals. Thus, it may be argued that this extensive data base provides a good understanding of the toxicological effects of a pesticide under a variety of exposure circumstances and allows a generally complete basis for projecting potential risks to the young.

The current multigeneration test protocol evaluates the integrity and performance of the male and female reproductive systems, including gonadal function, mating behavior, conception, gestation, parturition, lactation and weaning, and the growth and development of the offspring. This study may also provide information about the effects of the test substance on neonatal morbidity and mortality and preliminary data on pre- and post-natal developmental toxicity. The parents are exposed continuously to the test agent prior to mating, during gestation, and during lactation. The progeny from this mating are also continuously exposed, weaned, allowed to mature and mate. This cycle is observed while the animals are dosed for two consecutive generations. Some of the observed changes may be the consequence of in utero or post-natal exposure. Many parameters are evaluated in this toxicity study which could identify adverse effects on the neonate, including body weight, and clinical and behavioral signs. Gross pathological examinations are performed on the parents, with histopathological examinations focusing primarily on the organs of reproduction. The reproduction study is believed to capture most of the major effects of a chemical seen on the neonate [7]. Generalized toxicity will also be observed during the more comprehensive chronic toxicity and/or carcinogenicity studies which require exposure to the animal over an extensive period of its lifetime.

2. Proposed test guideline revisions

A developmental neurotoxicity test guideline was published in the Federal Register in l99l (USEPA, 1991c). Since that time, the Agency has requested that this developmental neurotoxicity testing be conducted as a conditional requirement for the registration of a small number of pesticides (approximately 10) based upon specific criteria confirmed by the FIFRA Scientific Advisory Panel (1987, 1994). A developmental neurotoxicity study should be mandatory if the data for a particular chemical demonstrate central nervous system malformations, and should be considered if the chemical has been shown to cause neuropathy/neurotoxicity in adults, is a hormonally active compound, or causes other types of developmental toxicity. These criteria are currently used in OPP to determine the need for a developmental neurotoxicity study for any chemical under review.

It is important to note that in one sense infants are given "overprotection" by the use of the reproductive NOEL in a two generation reproduction study for risk assessment. The method of fetal exposure/pup feeding during pregnancy/lactation results in excessive exposure to test compound during this period. It is known that pregnant/lactating dams consume 2 to 4 times the normal amount of food consumed prior to pregnancy. Thus, the dosage of test compound is proportionately increased in the blood supply. Further, offspring are often doubly exposed to the pesticide through compound excretion in the milk supply plus direct consumption of feed containing pesticide intended for the mother (pups start eating increasing amounts of the dam's food supply around lactation days 14 to 21)) (Shirley, 1984; Hanley and Watanabe, 1985).

In the developmental neurotoxicity study, the period of exposure is continuous through the last two-thirds of gestation, and parturition until postnatal (PN) day 10. The pups are evaluated for physical landmarks of maturation, reflex development, motor activity, sensory function, and learning and memory. Tissues of the nervous system are examined histopathologically for pups on PN day 11, and young adults on PN day 60.

There are some parameters which are not currently evaluated in the current developmental or reproductive toxicity testing guidelines (e.g., continued dosing up to termination of a developmental toxicity study to evaluate reproductive effects, or changes in sperm morphology and motility). However, OPP has received data from registrants on a voluntary basis addressing some of these parameters, which we have in turn used for risk assessment. As a consequence, the Agency became aware of the merit of these data and is now including these parameters in the revised data requirements. The new test guidelines for reproductive and "pre-natal developmental toxicity [8]" are in the last stages of public comment and finalization. Recommendations of the NAS committee and many others have been incorporated to clearly identify sensitive endpoints that relate to pre-natal and post-natal development. The "pre-natal developmental toxicity testing guideline" recommends that the test substance be administered daily to the pregnant dams from the day of implantation (approximately gestation day 6) through termination of the study. Termination in this study will be around day l8 for mice, day 20 for rats and day 29 for rabbits. Late-developing systems in the maturing fetus (e.g., the reproductive system or some aspects of the CNS), will be exposed to the test substance under the new developmental toxicity testing guidelines.

In the new reproduction testing guideline, estrous cyclicity will be evaluated in adult females and sperm will be examined in adult males at study termination; sperm motility, total sperm count, and morphology will be assessed. As stated previously, these endpoints have not received attention in previous Agency guidelines. In addition, the timing of sexual maturation (puberty) now will be examined in the offspring of both generations, and a selection of reproductive organ weights will be taken for all parents. These additions will increase the ability of the reproduction study to identify additional hazards in the developing and maturing animal.

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[8] The new harmonized test guidelines designation, "prenatal developmental toxicity" refers to a study which evaluates only those aspects of developmental toxicity up to the time of birth. This study, together with the multigeneration study, and in some cases the developmental neurotoxicity study, give a more complete picture of prenatal and postnatal exposure.

3. Potential limitations of test requirements

The developmental toxicity, the developmental neurotoxicity and reproduction toxicity studies cover most of the comparable exposure periods experienced by infants and children. It should be noted, however, that although it is believed that xenobiotics may be transferred from the mother to the pre-weaning offspring via the milk, these studies do not include quantitation of the levels of such an exposure. Furthermore, the data generated under these testing guidelines do not include measurements of the parent chemical or its metabolites in the milk. Another confounding factor is that towards the middle of the lactation period, the pups may have two sources of exposure to the test article (e.g., milk and the mother's chow) (which is not quantified). The lack of this information impairs the Agency's ability to provide, a more accurate hazard/risk assessment for infants.

V. Conclusions and Recommendations

The FQPA requirement that an extra uncertainty factor (up to 10X) be applied to the endpoints of concern in the reproduction or developmental toxicity study to protect the neonate and maturing individual is a prudent and conservative step on a case-by-case basis under special circumstances. The following are examples of when an additional UF may be applied.

1. When the severity of the effect, the potency or unusual toxic properties of a compound make determination of the adequacy of the uncertainty factors difficult due to the shape of the dose response curve(s).

2. The chemical has an incomplete data base.

The blanket use of an additional 10-fold uncertainty factor for every pesticide, regardless of the outcome of the reproduction and developmental studies as currently conducted is unwarranted, and was not recommended by the NAS report.

In the near future, the U.S. EPA will finalize the new reproduction and "pre-natal developmental" test guidelines. They will improve the Agency's ability to assess the unique sensitivities of the developing fetus and maturing individual. One possible shortcoming in the risk characterization of increased susceptibility of infants and children is the inability to address enhanced sensitivity of a subpopulation of infants, or infants that are being exposed through other routes (.e.g., skin, inhalation) during the first years of life. Active research in

this area is currently being conducted by Dr. Robert Chapin at NIEHS using a special post-natal protocol to examine selected pesticides of special concern. This research should provide valuable insights into unique neonate/infant sensitivities.

The Pesticide Program in concert with its stakeholders proposes to: 1) adopt the draft revisions to the prenatal and reproduction study guidelines as soon as possible to improve identification of pre- and post-natal hazards, 2) continue to carefully evaluate each pesticide chemical using the criteria described earlier in the paper (under section II) with respect to any effects on the fetus, the neonate and the young individual, 3) continue to interact with ORD, other agencies or join with stakeholders in developing protocols to evaluate exposure of pre-weaning animals to pesticides by oral, dermal and inhalation routes, and 4)continue to support the development and execution of a research plan to characterize age-related differences which may exist as a consequence of exposure to pesticides.

APPENDIX 1

Taken from Section 9.2.2 EHC 104 (WHO, 1990)

Modifications of uncertainty (safety) factors to either increase or decrease their size are based upon the following principles:

1. When relevant human data are available, the 10-fold factor for inter-species variability may not be necessary. However, relatively few parameters are studied in man in the assessment of pesticide safety, and data on oncogenicity, reproduction and chronic effects are rarely available. Thus, even if the parameter measured in humans is the same as the most sensitive adverse effects measured in the experimental animal (e.g., erythrocyte cholinesterase depression), uncertainty still remains with respect to the potential effects on other parameters. This usually necessitates an increased safety factor. Consequently, JMPR rarely utilizes safety factors as low as 10-fold.

2. The quality of the data supporting the NOAELs determined in the animal experiments (and also in human experiments) influences the choice of the safety factor. Unfortunately, toxicity studies are rarely perfect in all respects. While a study may serve to answer a basic question, the degree or certainty with which the question is answered may be reduced by, for example, increased mortality in all groups in an oncogenicity study, resulting in marginally-acceptable data being available at the termination of the study. When a request for a repeat study is not fully justified, an increased safety factor may be utilized under such circumstances.

3. The quality of the total data base may affect the choice of safety factor. Significant data deficits may warrant an increased safety factor due to increased uncertainty.

4. The type and significance of the initial toxic response may alter the safety factor. Thus a response which is reversible may result in a reduced safety factor.

5. The limited number of animals used in oncogenicity studies limits the sensitivity of the study in the identification of a threshold dose. When evidence of neoplasia has been identified, safety factors may be increased depending on the available ancillary data and the establishment of an NOAEL.

6. The shape of the dose/response curve (in those cases where data are adequate to permit derivation of such a curve) may also be considered in assessing safety factors.

7. Metabolic considerations may influence the choice of the safety factor. Thus, saturation of metabolic pathways resulting in toxic manifestations, biphasic metabolic patterns, and data on comparative metabolism may all affect the magnitude of the safety factor.

8. Knowledge of the comparative mechanisms of toxic action in experimental animals and man may influence the choice of safety factor.

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